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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/954,954	10/21/1997	NEENA L. SUMMERS	2991/1	6756

7590 01/08/2004

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EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/954,954	SUMMERS ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after a decision by the Board of Patent Appeals and Interferences, but before the filing of a Notice of Appeal to the Court of Appeals for the Federal Circuit or the commencement of a civil action. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 14 October 2003 has been entered.

Status of Application, Amendments, And/Or Claims

The amendment filed 14 October 2003 has been entered in full. Claim 1 has been amended. Claim 3 is indicated as amended, but does not actually appear to have been amended. Claims 1-14 are under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. § 103

Claims 1, 5 and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. (U.S. Patent 5,635,599) in view of Wen et al. (1993, Blood 82:1507-1516).

Pastan et al. teach growth factor receptor agonist polypeptides and nucleic acids encoding same, comprising a modified growth factor amino acid sequence, wherein the modification comprises the linear rearrangement wherein the N-terminus is joined to the C-terminus directly or through a linker capable of joining the N-terminus to the C-terminus and having new C- and N-termini in the middle of the polypeptide (Fig. 1; column 2, brief description of Fig. 1; column 3, lines 35-53). Pastan et al. teach that erythropoietin (EPO) is amenable to this procedure, which they term "circular permutation" (column 4, lines 30-42). Preferred linkers are discussed at column 7, as including GGNGG, and GGGNGGG. Pastan et al. teach a method of recombinantly producing the circularly permuted ligand (column 9, line 62 to column 10, line 15). Pastan et al. also teach a compositions comprising the circularly permuted growth factor, complementary growth factors, and a pharmaceutically acceptable carrier (columns 16-17). Pastan et al. disclose other hematopoietic growth factors, including GM-CSF, G-CSF, M-CSF, IL-1, IL-2, IL-3, IL-4, IL-6 and IL-7 (col. 5, lines 27-44). Pastan et al. teach a method of stimulating production of target cells comprising administering the circularly permuted growth factor to a patient (col. 16, line 26 to col. 18, line 33).

Pastan et al. do not disclose a working example of circularly permuted EPO, nor do they disclose a sequence of EPO. However, human EPO had been previously characterized (Wen et al., p. 1512, Figure 6). Pastan et al. disclose that a good choice for an "opening site" (i.e., a new C- and N-termini) is at a site that is tolerant to amino acid substitution or in a region of the protein that does not show highly conserved

sequence identity between closely related proteins in an alignment (column 8, lines 30-54). Wen et al. in Figure 6 align human, Cynomolgous monkey, Rhesus monkey, mouse, rat, sheep, pig, cat and dog EPO sequences. All are functional. Substitutions occur at amino acid positions 33, 34, 35, 36, 50, 54, 55, 57, 58, 77, 84, 111, 118, 119, 120, 123, 124, 125, 126, 127 and 128. This suggests that an opening site would be tolerated in a circularly permuted EPO molecule at any one of these sites.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the circularly permuted growth factors, DNA encoding same, methods of recombinantly producing same, pharmaceutical compositions comprising same and methods of administering same as taught by Pastan et al., and to modify that teaching by extending it to EPO molecules disclosed by Wen et al., with opening sites at amino acid positions 33, 34, 35, 36, 50, 54, 55, 57, 58, 77, 84, 111, 118, 119, 120, 123, 124, 125, 126, 127 and 128. A reasonable expectation of success is given by Pastan et al.'s disclosure that preferred opening sites are those which can tolerate amino acid substitution and Wen et al.'s disclosure of substitution toleration at positions amino acid positions 33, 34, 35, 36, 50, 54, 55, 57, 58, 77, 84, 111, 118, 119, 120, 123, 124, 125, 126, 127 and 128. The motivation to do so is provided by Pastan et al. in their express suggestion to extend the teachings to EPO.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

Note the comment by the Board of Appeals and Interferences at p. 4, footnote 1, of the Decision on Appeal in this application (Paper No. 34, 13 August 2003).

Specifically, the Board noted that "given that the claim is written in Markush format the combination of references only has to suggest the modification of one of these sites." In the instant rejection, twenty one of the forty nine sites listed in the claims are suggested by the combination of references.

Claims 1-4 and 6-9 rejected under 35 U.S.C. 103(a) as being unpatentable over Pastan et al. in view of Wen et al. as applied to claims 1, 5 and 10-14 above, and further in view of Chaudhary et al. (1989, Nature 339:394-397) and Cousens et al. (U.S. Patent 4,751,180).

Pastan et al. in view of Wen et al. teach circular permuteins of EPO embraced by claim 1, for example. Neither reference teaches the specific GlySer-rich linker sequences as required by claims 2-4 and 6-9.

Chaudhary et al. disclose the use of a 45 base pair linker for connecting two antibody variable domains in a fusion protein. The linker encoded a 15 residue long stretch of Gly and Ser residues, see Fig. 1a. Cousens et al., disclose that non-polar amino acids such as Gly and Ser are useful for a flexible linker (column 4).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the circular permuteins of EPO as taught by Pastan et al. in view of Lin, and to modify that combined teaching by using GlySer-rich flexible linkers between the two portions of the circular permuteins as taught by Chaudhary et al. and Cousens et al. with a reasonable expectation at successfully achieving a circular permutein with sufficient flexibility in the linker for the two portions of

the circular permutein to fold favorably for retained function. The motivation to do so is provided by the disclosures of Chaudhary et al. and Cousens et al. which disclose that the flexible linkers do not destroy activity.

Thus, the claimed invention as a whole was very clearly *prima facie* obvious over the prior art.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed invention wherein the new C- and N-termini are crested between the amino acid residue pairs of SEQ ID NO: 121 selected from the group consisting of:

33-34	50-51	56-57	110-111	119-120	125-126
34-35	53-54	57-58	111-112	122-123	126-127
35-36	54-55	77-78	117-118	123-124	127-128 and
36-37	55-56	84-85	118-119	124-125	128-129;

does not reasonably provide enablement for the claimed invention wherein the new C- and N-termini are crested between the amino acid residue pairs of SEQ ID NO: 121 selected from the group consisting of:

23-24	45-46	86-87	131-132.
28-29	46-47	108-109	
37-38	47-48	109-110	
38-39	48-49	112-113	
40-41	51-52	113-114	
41-42	52-53	114-115	
43-44	78-79	129-130	
44-45	85-86	130-131 and	

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly directed to human erythropoeitin (EPO) receptor agonist polypeptides that are circular permuteins of natural human EPO, optionally with a linker between the two halves of the EPO circular permutein, and optionally modified by removal of one or two N-terminal amino acid residues. Claims are also presented to nucleic acids encoding the EPO circular permuteins, methods of recombinantly producing the EPO circular permuteins, compositions comprising the EPO circular permuteins and a pharmaceutically acceptable carrier, and a method of stimulating the production of hematopoietic cells in a patient comprising administering the EPO circular permuteins to a patient.

The specification discloses a sequence of human EPO, and describes methods by which to make the recited EPO circular permuteins. However, the specification does not disclose any working examples wherein the EPO circular permuteins were tested for EPO agonist, or hematopoietic, activity as required by the claims.

The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure as set forth in the specification for the following reasons.

Preliminarily, the examiner acknowledges that patent law has long established that Applicant may claim a genus of products encompassing a reasonable number of inoperative embodiments. In the instant case, 25 out of 49 species recited in claim 1 are deemed non-enabled, and thus the claims do not fall under this protection. The claims must be analyzed for scope of enablement.

The prior art teaches several criteria for choosing opening sites when making active circular permuteins from growth factors such as EPO. See Pastan et al., *supra*, col. 7-9, wherein it is taught that:

> If the new termini interrupt a critical region of the native protein, activity may be lost (col. 7, li. 8+). ... one may infer that the highly conserved sequences are critical for biological activity (col. 8, li. 45+).

Wen et al., *supra*, teach that residues 23, 24, 28, 29, 37-49, 51-53, 56, 78, 79, 85-87, 108-110, 112-115, 117 and 129-132 are conserved among nine mammalian EPO sequences.

Therefore, one skilled in the art would reasonably expect that EPO circular permuteins having an opening site at one of these residues would not have biological activity. The specification and evidence of record do not show otherwise.

Due to the large quantity of experimentation necessary to make and test the EPO circular permuteins deemed non-enabled above for the required EPO activities, the lack

of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the contradictory state of the prior art, the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (703) 308-2673. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne L. Eyler, Ph.D. can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

ECK